## REMARKS

Claims 1-133 appear in this application for the Examiner's review and consideration. Claims 20-95, 97-100, 102-105, 107-110 and 114-125 have been withdrawn by the Examiner as allegedly being drawn to non-elected subject matter.

Applicants note with appreciation that the Office Action Summary and page 10, paragraph 3 of the Office Action state that claims 1-19, 96 and 111-129 are allowed. Applicants wish to bring to the Examiner's attention that claims 114-116 depend, directly or through intervening claims, on independent claim 20; claims 117-119 depend, directly or through intervening claims, on independent claim 39; claims 120-122 depend, directly or through intervening claims, on independent claim 58; and claims 123-125 depend, directly or through intervening claims, on independent claim 77.

Favorable reconsideration of the claims in view of the remarks herein is respectfully requested.

## Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 101, 106 and 130-133 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly not enabled. Applicants respectfully traverse.

The enablement requirement of § 112 demands that the patent specification enable "those skilled in the art to make and use the full scope of the claimed invention without 'undue experimentation.' " *Genentech, Inc. v. NovoNordisk,* 108 F.3d 1361, 1365, 42 U.S.P.Q.2d 1001, 1004 (Fed. Cir. 1997) *(quoting In re Wright,* 999 F.2d 1557, 1561, 27 U.S.P.Q.2d 1510, 1513 (Fed. Cir. 1993)). Factors to be considered when determining whether experimentation is undue include: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *In re Wands*, 858 F.2d 731, 737, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988).

When rejecting a claim under the enablement requirement of § 112, the PTO bears an initial burden of setting forth a reasonable explanation as to why it is not adequately enabled by the description of the invention provided in the specification of the application. This

includes providing sufficient reasons for doubting any assertions in the specification as to the scope of enablement. *In re Wright,* 999 F.2d 1557, 1562, 27 U.S.P.Q.2d 1510, 1513 (Fed. Cir. 1993).

1. **Claims Reciting Methods for Inhibiting VR1 Function**

In connection with claims 106, 132 and 133, Applicants submit that these claims are directed to methods of inhibiting VR1 function in a cell. The methods comprise contacting a cell capable of expressing VR1 with an effective amount of a hydroxyiminopiperazine compound of the invention. The specification teaches those in the art how to make and use the invention as broadly as it is claimed without undue experimentation. In particular, the specification, *inter alia*, at pages 136-146 and pages 173-178, provides multiple schemes and working examples of how to make the hydroxyiminopiperazine compounds of the invention. The specification, *inter alia*, at pages 186-189, teaches assays for determining binding of the hydroxyiminopiperazine compounds of the invention to VR1. Furthermore, assays for VR1 inhibiting properties are well known in the art, *e.g.*, the calcium mobilization assay used in Szallasi et al., *Molec. Pharmacol.* 56:581-587 (1999), a copy of which is provided in the Supplemental Information Disclosure Statement filed herewith. "A patent need not teach, and preferably omits, what is well known in the art." *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 231 U.S.P.Q. 81 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987); *Paperless Accounting, Inc. v. Bay Area Rapid Transit Sys.*, 804 F.2d 659, 231 U.S.P.Q. 649 (Fed. Cir. 1986) ("A patent need not include in the specification that which is already known to and available to the public."). Since the specification teaches how to make the hydroxyiminopiperazine compounds of the invention, how to assay for binding of the hydroxyiminopiperazine compounds of the invention to VR1, and assays for VR1 inhibiting properties are well known in the art, the specification teaches those in the art to use the invention commensurate in scope with these claims.

Additionally, Applicants provide examples which demonstrate that a hydroxyiminopiperazine compound of the present invention, Compound A1(a) (page 65, Example 3 on page 176 of the specification), is capable of and actually does inhibit VR1. For example, in the pH-based assay for VR1 modulating properties described in detail in Example 16, Compound A1(a) was determined to have an $IC_{50}$ of 40.9 ± 16.7 nM (n = 4) (page 188, lines 22-23). Additionally, in the capsaicin-based assay of Example 16, Compound A1(a) was determined to have an $IC_{50}$ of 58.3 ± 10.1 nM (n = 4) (page 189, lines

3-4). These results demonstrate that Compound A1(a), an illustrative hydroxyiminopiperazine compound, binds to and modulates the activity of human VR1.

According to applicable law, under 35 U.S.C. § 112 an inventor is not required to disclose a test of every species encompassed by their claims. *In re Angstadt*, 190 U.S.P.Q. 214, 218 (C.C.P.A. 1976) (emphasis in original).

Moreover, the present Office Action has conceded that "the instant compounds interact with vanilloid receptor" (page 4, final paragraph) and the "instant compounds are disclosed to have inhibiting vanilloid receptor activity." (page 6, line 14).

Accordingly, Applicants respectfully request that, as the Office Action has not met its initial burden of setting forth a reasonable explanation as to why there is not adequate enablement provided by the description of the invention in the specification, the rejection of claims 106, 132 and 133 under 35 U.S.C. § 112, first paragraph be reconsidered and withdrawn.

**2. Claims Reciting Methods for Treating Pain**

In connection with claims 101, 130 and 131, Applicants submit that these claims are directed to a method for treating pain. The methods comprise administering to an animal an effective amount of a hydroxyiminopiperazine compound of the invention. The Office Action admits, on page 4, that the specification is "enabling for treating pain due to headache or arthritis." In other words, the Office Action seeks to limit the claims to specific embodiments in the specification. Applicants submit that claims need not be limited to the examples in the specification. In *In re Goffe*, 542 F.2d 564, 567, 191 U.S.P.Q. 429, 431 (C.C.P.A. 1976), the court stated:

> [T]o provide effective incentives, claims must adequately protect inventors. To demand that the first to disclose shall limit his claims to what he has found will work or to materials which meet the guidelines specified for "preferred" materials in a process such as the one herein involved would not serve the constitutional purpose of promoting progress in the useful arts.

Contrary to the allegations in the Office Action that the specification only enables treatment of pain due to headache or arthritis, Applicants respectfully point out that it is known in the art that VR1 antagonism is associated with the prevention of pain. For

example, each of the following three references discloses that VR1 antagonism has been associated with the prevention of pain: R. Wrigglesworth and C. Walpole, "Capsaicin-like Agonists," *Drugs of the Future*, 23(5):531-38 (1998); S. Bevan and P. McIntyre, "Vanilloid Receptors: Pivotal Molecules in Nocciception," *Current Opinions in CPNS Investigational Drugs*, 2(2):178-85 (2000); and A. Szallasi and P. Blumberg, "Vanilloid (Capsaicin) Receptors and Mechanisma," *Pharmacology Reviews*, 51(2):159-211 (1999); a copy of each is provided in the Supplemental Information Disclosure Statement filed herewith.

It is also recognized in the literature that VR1 antagonists may be useful for the treatment of inflammatory hyperalgesia and pain. *See*, e.g., page 744 of Lopez-Rodriquez et al., *Mini-Revs in Medicinal Chem.* 3(7):729-48 (2003), a copy of which is provided in the Supplemental Information Disclosure Statement filed herewith. Hence, the art does not limit VR1 as a target for the treatment of only headache and/or arthritis pain caused by a particular type of disease as alleged by the Office Action. Accordingly, the specification provides sufficient guidance to one skilled in the art that VR1 is useful target for treatment of pain caused by diverse disease conditions.

The Office Action alleges, on page 5, that the rejected claims embrace "any or all pain arising from various diseases and disorders as mediated by vanilloid receptor for which there is no enabling disclosure." According to applicable law, under 35 U.S.C. § 112, a specification which contains a teaching of how to make and use the invention must be taken as enabling unless there is reason to doubt the objective truth of the teachings which must be relied on for enabling support. *In re Marzocchi*, 439 F.2d 220, 223, 169 U.S.P.Q. 367, 369 (C.C.P.A. 1971), *In re Brana*, 51 F.3d 1560, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). As discussed above, the specification teaches how to make the hydroxyiminopiperazine compounds of the invention and the specification, *inter alia*, at pages 146-147, teaches that the hydroxyiminopiperazine compounds can be used to treat various types of pain. In particular, the specification, *inter alia*, at pages 179-182, provides prophetic examples of *in vivo* assays for using the hydroxyiminopiperazine compounds of the invention for treating various types of pain, such as acute pain, inflammatory pain, and neuropathic pain. Since the specification teaches assays for not only a single type of pain but various types of pain, the specification enables the methods of using the hydroxyiminopiperazine compounds of the invention for the treatment of a spectrum of pain (specification on pages 180, line 6 to page 182, line 31). Since the standard for enablement is from the view of one skilled in the art, the

assay provided in the specification is consistent with the scope of the claims. Hence, one skilled in the art, when considering the teaching of the present invention, would appreciate that the hydroxyiminopiperazine compounds of the present invention may be used to treat various types of pain arises from a range of conditions. Also, as discussed above, since the art does not limit the use of VR1 as a target to a particular pain arising from a particular disease, such limitation should not be imposed on the present claims. Hence, the specification enables the full scope of the claims.

The Office Action alleges, on page 9, that Applicants "have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use for treating any or all pain arising from any or all disease or disorders of the instant compounds." According to applicable law, under 35 U.S.C. § 112 an inventor is not required to disclose a test of every species encompassed by their claims even in an unpredictable art. *In re Angstadt*, 190 U.S.P.Q. 214, 218 (C.C.P.A. 1976) (emphasis in original). An invention is enabled even though the disclosure may require some routine experimentation to practice the invention. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 U.S.P.Q. 81, 94 (Fed. Cir. 1986). Applicants submit that the law does not require evidence or tests to show that the pharmaceutical use for treating "any or all pain arising from any or all disease or disorders" to satisfy the enablement requirement. All that is required is that one skilled in the art when provided with the specification is able to make and use the invention without undue experimentation.

Contrary to the Office Action's allegation, Applicants submit that the specification does provide specific assays that are widely accepted in the art for treatment of various types of pain using the hydroxyiminopiperazine compounds of the invention. Specifically, the examples teach assays for using the hydroxyiminopiperazine compounds of the invention for the treatment of pain that are well know in the art for quantifying:

- acute pain; (D'Amour et al., 1941, *J. Pharmacol. Exp. Ther.* 72:74-79 and the"Acute Pain" portion of Example 12 at pages 179-180 of the specification);
- inflammatory pain; (Bartho et al., 1990, *Naunyn-Schmiedeberg's Archives of Pharmacol.* 342:666-670 and the "Inflammatory Pain" portion of Example 12 at page 180 of the specification);

- neuropathic pain via the Seltzer model; (Seltzer et al., 1990, *Pain* 43:205-218) and the "Neuropathic Pain" portion of Example 12 at pages 180-181 of the specification); and
- neuropathic pain via the Chung model; (Kim, 1992, *Pain* 50(3):355-363 and the "Neuropathic Pain" portion of Example 12 at pages 181-182 of the specification).

The specification also teaches the Freund's complete adjuvant model of inflammatory pain, which is recognized in the art as associated with the development of persistent inflammatory mechanical hyperalgesia and provides reliable prediction of the anti-hyperalgesic action of clinically useful analgesic drugs (page 180, lines 6-24 of the specification). These assays are understood by one skilled in the art to be predictive for pharmaceutical use of compounds and for treatment of wide range of pain. Hence, the specification provides assays that are highly predictive for the pharmaceutical use for treating pain from various diseases and disorders.

Where a disclosure provides considerable direction and guidance on how to practice the invention, and where, at the time of the application, the skill in the art was quite high and the methods needed to practice the invention well known, a conclusion of enablement should be made. *In re Wands*, 858 F.2d 731, 740, 8 U.S.P.Q.2d. 1400, 1406 (Fed. Cir. 1988). Put another way, as Judge Rich explained in *In re Vaeck*, 20U.S.P.Q.2d 1438, 1445 (Fed. Cir. 1991), the statutory enablement requirement is satisfied if the specification "adequately guides the worker to determine, without undue experimentation, which species among all those encompassed by the claimed genus possess the disclosed utility" (emphasis added). Since the specification provides reasonable amount of guidance and direction to determine how to treat various types of pain with the hydroxyiminopiperazine compounds of the invention, without undue experimentation, the enablement requirement is fully satisfied. *See In re Wands*, 8 U.S.P.Q.2d at 1404, *Ex parte Mark*, 12 U.S.P.Q.2d 1904, 1906-1907 (B.P.A.I. 1989).

On one hand, the Office Action alleges, on page 9, that the specification "has no working examples to show treating any or all pain" and "the effects of inhibiting vanilloid receptor activity are unpredictable and at best limited to modulation of rheumatoid arthritis" while, on the other hand, page 4 of the Office Action admits that the specification is enabling for treating pain due to headache or arthritis. The Office Action does not provide any basis for the assertion that the methods of the present invention should be limited to pain due to a

particular condition. Applicants submit that the "Examiner should never make the determination [regarding enablement] based on personal opinion." MPEP 2164.05 (emphasis in original). To the extent that this rejection is based on facts within the Examiner's personal knowledge, Applicants request that the Examiner provide an affidavit pursuant to the provisions of 37 C.F.R. § 1.104(d)(2).

The specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation. *In re Borkowski*, 422 F.2d 904, 164 U.S.P.Q. 642, 645 (C.C.P.A. 1970). Since only an enabling disclosure is required, Applicants need not describe all actual embodiments. And, as discussed above, Applicants' invention need not be limited to an embodiment described in the specification. Applicants submit that the specification, *inter alia*, on pages 179-182, discloses prophetic examples related to *in vivo* assays for the treatment of pain. For a claimed genus, representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if one skilled in the art would expect the claimed genus could be used in that manner without undue experimentation. MPEP 2164.03. Furthermore, as discussed above, since the art does not limit the use of VR1 as a target for the treatment of a particular type of pain, the specification provides sufficient guidance to enable one skilled in the art to use the invention commensurate with the scope of the claims. The scope of enablement only need to bear a "reasonable correlation" to the scope of the claims. *See, e.g., In re Fisher*, 427 F.2d 833, 839, 166 U.S.P.Q. 18, 24 (C.C.P.A. 1970). A rigorous or an invariable exact correlation is not required, as stated in *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 U.S.P.Q. 739, 747 (Fed. Cir. 1985). Applicants submit that the *in vitro* and *in vivo* animal model examples as disclosed in the specification provide sufficient guidance to enable one skilled in the art to use the invention commensurate with the scope of the present claims.

The Office Action alleges, on page 7, that there are various forms of inflammation and that there is "no common mechanism by which all, or even most, inflammations arise." The Office Action further alleges the present claims are not enabled because "treatments for inflammation are normally tailored to the particular type of inflammation present, as there is no, and there can be no 'magic bullet' against inflammation generally." Applicants submit that claims 101, 130, and 131 are directed to treatment of pain that are associated with a condition, which is different from treatment of the condition itself. Thus, whether

inflammation is caused by various mechanisms is irrelevant to whether the method of treatment of pain caused by a condition, e.g., inflammation, is enabled.

The Office Action alleges, on page 8, that Dogrul et al., Di Marzo et al., and Foley are indicative of further future experimentation, and hence are "indicative of the requirement for undue experimentation." Applicants respectfully disagree. The Applicants are unable to locate in these references the Office Action's allegation. Applicants submit that Dogrul et al. teaches $mGLUR_5$ as a target for neuropathic pain, Di Marzo et al. recognizes VR1 as a promising therapeutic strategy for novel analgesic drugs, and Foley teaches the management of pain. Applicants further submit that a suggestion of further future experimentation does not mean that experimentation is undue. The law permits a considerable amount of experimentation if it is merely routine or the specification provides reasonable amount of guidance and direction to the experimentation. *In re Jackson*, 217 U.S.P.Q. 804, 807 (1982).

The Office Action alleges, on page 9, that the "quantity of experimentation needed would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan." As discussed above, since the specification teaches how to make and use the compounds of the invention and the experimentation is routine, a considerable amount of experimentation is permissible.

The Office Action, citing to Valenzano et al. and Szallasi et al., alleges, on page 8, that "treating disease or disorders by the inhibition of vanilloid receptor is still exploratory." Applicants submit that neither of these references is relevant to the state of the art relating to the above-identified application, filed September 23, 2003, because each published in 2004. Applicants also submit that the "exploratory" factor is irrelevant in the determination of enablement. *See Plant Genetic Sys., N.V. v. Dekalb Genetics Corp.*, 315 F.3d 1335, 1339, 65 U.S.P.Q.2d 1452, 1455 (Fed. Cir. 2003) (alleged "pioneer status" of invention irrelevant to enablement determination). Furthermore, contrary to the Office Action's allegation, as discussed above it has been recognized in the art that VR1 antagonists may be useful for the treatment of inflammatory hyperalgesia and pain. *See*, e.g., page 744 of Lopez-Rodriquez et al., *Mini-Reviews in Medicinal Chemistry* 3(7):729-48 (2003). It is also recognized in the art that there is a role for VR1, *e.g.*, in persistent and chronic pain arising from inflammation or nerve injury. Pomonis et al., *J. Pharmacol. Exper. Therapeutics* 306(1):387-393 (2003) ("Pomonis," a copy of which is provided in the Supplemental Information Disclosure

Statement filed herewith). VR1 was found to play a role in the pathology of chronic pain, both of inflammatory and neuropathic origin (see Pomonis page 392). Applicants submit that the statutory enablement requirement is satisfied since the specification adequately provides guidance to one skilled in the art of how to make the hydroxyiminopeperazine compounds of the invention and how to assay for the treatment of various types of pain.

Accordingly, Applicants respectfully request that, as the Office Action has not met its initial burden of setting forth a reasonable explanation as to why there is not adequate enablement provided by the description of the invention in the specification, the rejection of claims 101, 130 and 131 under 35 U.S.C. § 112, first paragraph be reconsidered and withdrawn.

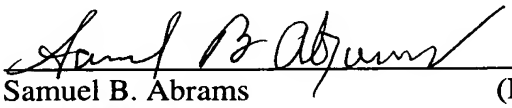
## CONCLUSION

In view of the foregoing remarks, Applicants respectfully submit that all of the rejections connected with claims 101, 106 and 130-133 should be withdrawn. Thus, reconsideration and early allowance of claims 101, 106 and 130-133 is respectfully requested.

Applicants believe that no fee is due in connection with this reply (other than for the accompanying Supplemental Information Disclosure Statement). However, should the Patent Office determine that a fee is due, please charge the required amount to Jones Day Deposit Account 50-3013.

Respectfully submitted,

Date: January 27, 2006



30,605
(Reg. No.)

Samuel B. Abrams
**JONES DAY**
222 East 41st Street
New York, New York 10017-6702
(212) 326-3939